Free mass drug administration for malaria elimination in Southern Mozambique? Evidence from a quasi-experimental evaluation applied to routine surveillance data

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Abstract

Without free distribution of essential health protecting technologies for malaria control and elimination, uptake has been shown to be poor in developing countries. We provide the first evidence outside of a clinical setting using surveillance data, on achievable effectiveness of a large-scale malaria elimination campaign combining universal indoor residual spraying and free door-to-door mass drug administration. During peak malaria season, incidence reduced by 91.3% (2016) and 81.3% (2017) relative to the control. Although short-term cost estimates reflect a high financial burden, the large positive externalities and long-term social and economic benefits of malaria elimination, indicate a highly cost-effective strategy over time.

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1. Introduction

In 2017, the global burden of malaria was estimated as 219 million cases and 435,000 deaths, with 90% of disease burden concentrated in Africa. Despite a persisting remarkable burden, major progress has been made, with an average decrease of 18% in incidence and 28% in mortality between 2010 and 2017 (World Health Organization, 2018). Recent improvements in preventive and treatment technologies, the rise in their coverage, and the knowledge accumulated by researchers, policymakers, healthcare providers and communities, has shifted the attention from malaria control to its elimination and global eradication (Liu, Modrek, Gosling, & Feachem, 2013).

The last major attempt at malaria eradication was in the 1950s where the World Health Organization's (WHO) Global Malaria Eradication Program (GMEP) eliminated the disease from North America and parts of South and Central America, Europe and the Caribbean. The campaign failed in sub-Saharan Africa (SSA) and was abandoned by 1969. The high incidence rate in SSA along with the high cost of elimination campaigns and emerging vector resistance to insecticides resulted in the policy recommendation of malaria control rather than elimination.

In September 2015, WHO's Malaria Policy Advisory Committee recommended for the first time the use of Mass Drug Administration (MDA) in combination with existing malaria control strategies (of long-lasting insecticide treated nets (LLINs) and indoor residual spraying (IRS)), for countries looking to eliminate malaria (Eisele et al., 2016; Hsiang et al., 2013; Newby et al., 2015; Poirot et al., 2013), including in Africa. With MDA, which is based on the principle of treatment and preventive chemotherapy, a full therapeutic course of safe and effective drugs is repeatedly distributed to the target population living in endemic areas, irrespective of the presence of symptoms or infection.

Concerns have been raised on the effectiveness and sustainability of free door-to-door MDA as a strategy for elimination of infectious diseases. This strategy is a form of medium-to-long term subsidy

where the additional high cost of free door-to-door distribution of MDA is experienced for a few years until the disease is eliminated in the region and is expected to be outweighed by the long-term economic and human capital benefits of elimination[2]. The main arguments against free distribution are two-fold: it can generate an anchoring effect to "zero or near-zero" cost and, therefore, lowering the long-term willingness to pay for the product; it could reduce the potential psychological effects of paying for a product and lead to underuse or wastage (P. Dupas, 2014). Both hypotheses against free distribution can be rejected under certain conditions: free distribution might increase long-term demand if the new technology is an experience good and individuals learn about the benefits from the true value of the product (P. Dupas, 2014); individuals receiving free health products are not less likely to use them than those who paid subsidized positive prices (Cohen & Dupas, 2010).

Even with free door-to-door distribution, there exist challenges to achieving and maintaining sustained coverage and compliance to MDA required to break transmission and move towards elimination. For example, difficult identification of private benefits and the very low opportunity for social learning over time. Individual benefits from MDA can be hardly assessed by recipients and MDA can be hardly considered as an experience good for a number of reasons: (i) some people refuse the first intake for mistrust; (ii) some people that are sick –either malaria or non-malaria related- before drug intake do not get well after MDA; (iii) people who are well at the moment of MDA may get worse due to side effects or remain well but with scarce understanding of the links between their good health and the drug intake. Coverage and compliance are additionally likely to decrease over time in the context of elimination where disease prevalence progressively decreases (Hauck, 2018). The reluctance to accept and take the drug at first and successive rounds may be resolved to some extent through community sensitization of the target population and by strictly monitoring coverage and compliance over time. Free distribution of MDA even within sensitized communities is therefore necessary but not guaranteed to obtain high MDA coverage and compliance in the long term.

[2] Previous studies have assessed the impact on economic indicators of malaria elimination campaigns in the 1950s (Barofsky, Anekwe, & Chase, 2015; Bleakely, 2010; Cutler, Fung, Kremer, Singhal, & Vogl, 2010; Lucas, 2010).

However, several empirical studies have demonstrated that without the free distribution of important health protecting technologies, uptake is poor in developing countries (P. Dupas, 2014; Nava, Berry, & Shapiro, 2010; Tarozzi et al., 2014). In the case of malaria, the focus of our study, evidence clearly shows that cost-sharing reduces uptake of insecticide treated bed nets (ITNs)(Cohen & Dupas, 2010), and lower product coverage with cost-sharing relative to free distribution, even when the product is offered on credit (Tarozzi et al., 2014). There are two main economic rationales for free distribution (or heavy subsidization) of malaria preventative technologies. First, given the infectious nature of the disease it prevents, products such as LLINs and indoor-residual spraying (IRS) generate positive health externalities, and without a subsidy private investment in them is socially suboptimal. Second, when the majority of the population is poor and credit-constrained, subsidies may be needed to ensure widespread access (Cohen & Dupas, 2010; Tarozzi et al., 2014). Consequently, since 2007, the World Health Organisation (WHO) has advocated the free distribution of LLINs and IRS as a malaria control strategy.

To our knowledge, there is no evidence on achievable effectiveness through long-term free door-to-door distribution of a new malaria health protecting technology in the context of elimination. Unlike the case of LLINs there is almost no evidence on the effectiveness of MDA in general and MDA for malaria elimination in SSA are few (Newby et al., 2015). MDA has been used only sporadically against malaria in most settings, and there is only one cluster-randomised trial on the effect of MDA on transmission (Eisele et al., 2016).

In this paper we provide evidence of the maximum achievable effectiveness of a public campaign of free door-to-door MDA (in combination with existing malaria control strategies of IRS and community sensitization) in a district of Southern Mozambique, where the disease is highly endemic, compared to a situation of only standard control strategies. Additionally, we present the costs of this campaign.

Our study is important for the following reasons: (1) To the best of our knowledge, this is amongst the first large scale studies to evaluate the effectiveness of intensified malaria control strategies for the purpose of elimination outside a clinical setting. Our estimates can be seen as an upper bound of what might be expected in terms of uptake and effectiveness when MDA is distributed free to sensitized communities. We show what levels of effectiveness can be achieved in the short and long term, with less than 100% uptake even with free door-to-door distribution of a new health protecting technology plus community sensitization activities and monitoring. Our outcome of interest is malaria incidence in children 0-4 years (the age group with the highest disease burden in Africa) and those 5 and over. Few studies have considered actual malaria indicators, many have focussed on adoption of preventive technologies. Malaria incidence is the best indicator of coverage and compliance with MDA. Evidence from LLIN studies show that uptake does not reflect usage and the only way to evaluate effectiveness is through malaria indicators.

(2) We demonstrate how routine surveillance data widely gathered under most National Malaria Control Programs (NMCPs) around the world can be used to evaluate the impact of such large-scale programs in the absence of randomised-controlled trials. The use of malaria surveillance data to ascertain progress towards elimination has been suggested also in Churcher et al. (2014). In that study, a simple method was suggested based on computing the proportion of imported cases among all detected cases. If the proportion lies below a specified threshold, imported cases cause shorter chains of transmission and the disease can be considered as close to local elimination. Therefore, the initiative can be considered "successful". While this method is valuable, the distinction between imported and local cases may not apply in many contexts, particularly in evaluations of initiatives (such as in our setting) which are implemented at the local (district) level and in areas of frequent cross-border activity. Furthermore, the approach of Churcher et al. (2014) is useful for monitoring elimination activities, but it does not estimate the causal impact of elimination activities.

Over two years (2016 and 2017), we find a 91.3% and 81.3% reduction in the incidence of malaria compared to our comparison group. While this total effect is large and positive it decreases over time and corresponds with lower uptake of the MDA over rounds. The larger effect in the first year corresponds with higher uptake and a drought in Mozambique in 2016. The large but lower effect in 2017 could be seen as evidence that the positive health spillovers may have dampened uptake of MDA in 2017. Regardless of the declining effectiveness, our study provides clear evidence that free door-to-door MDA within a sensitized population in combination with control strategies in the context of elimination, results in a large reduction in the malaria burden, clearly moving towards elimination.

The rest of this paper is organized as follows. Section 2 describes the intervention implemented in Mozambique. Section 3 describes the data and Section 4 the methods. Section 5 presents the results and Section 6 discusses the findings, including highlighting study limitations.

2. Context – Malaria elimination campaign in Mozambique

Mozambique is one of the 10 countries in the world with the highest burden of malaria. According to official health facility-based data, in Mozambique there are over 7.8 million cases and about 2,500 malaria-related deaths every year (World Health Organisation, 2015).

As a member of the Elimination 8 initiative, the country has increased its regional collaboration in order to accelerate progress towards elimination. Cross-border collaboration is especially crucial for Mozambique, as it borders with six other malaria endemic countries, some of them already in pre-elimination stages. Renewed regional efforts began in 2015 with the establishment of an intergovernmental initiative among Mozambique, South Africa and Swaziland (MOSASWA) with the goal of accelerating the transition from pre-elimination to elimination in the latter two countries and from control to pre-elimination in the South of Mozambique by 2020.

As part of the renewed regional interest in malaria elimination (Moonasar et al., 2016), Mozambique has engaged in a five-year program with the objective of eliminating malaria in the South of the country by 2020. To that end, the Mozambican Alliance Towards the Elimination of Malaria (MALTEM) and the Malaria Technical Advisory Committee were created in 2015.

The elimination initiative began with the district of Magude, Maputo province. Magude was chosen because of its representativeness as an area endemic of malaria (in 2014, the incident rate was 252 per 1,000 population), and because of its proximity to the Manhiça Health Research Centre (CISM), the implementing organization.

The malaria elimination package in Magude was deployed before the rainy season in 2015-16 and 2016-17, and consisted of (i) comprehensive vector control through universal IRS, (ii) community sensitization around MDA and two monthly population-wide MDA rounds with Dihydroartemisinin-Piperaquine (DHA/PPQ)[3] and (iii) a comprehensive epidemiological surveillance system.

3. Data

We use data extracted from Mozambique's *Boletim Epidemiológico Semanal (BES),* the epidemic disease reporting system used by the NMCP. It gathers data on weekly number of clinical cases for several infectious diseases, including malaria. BES reports the number of confirmed (either by rapid diagnostic test or microscopy) malaria cases by week and age group (children under 5 years and those aged 5 and above). We use population estimates from the National Statistical Institute (INE) for the two age groups to create our primary outcome: weekly malaria incidence rate (cases per 1000 population at risk) for under 5 years (<5) and 5 plus years (5+).

Our treatment group is the district of Magude, Maputo province. The comparison group consists of the other districts in Maputo province, as well as the districts from the neighbouring province, Gaza

[3] DHA/PPQ is the drug recommended by the WHO for malaria elimination. Its efficacy has been demonstrated in several clinical trials (Naing et al., 2013).

(see Figure 1). We excluded Manhiça district from the analysis, as part of the district also received the MDA in 2016-17 and because Manhiça is where most malaria research has been carried out over the past 20 years by CISM. The selection of control districts from locations around Magude is to ensure treatment and control groups have similar epidemiological characteristics. In addition, our analysis uses variables as predictors of malaria incidence: coverage of long-lasting insecticide treated bednets (LLINS), average weekly temperature and weekly precipitation.

We retrieved weather data for all weather stations in Mozambique for the last decade from the National Oceanic and Atmospheric Administration (NOAA) and used a simple interpolation method to estimate local weather for each district centroid. For each district centroid on each date and for each weather indicator (temperature, precipitation), a weighted mean of that indicator was calculated from all Mozambican weather stations, with the weight being equivalent to 1 divided by the distance (in kilometres) from the district's centroid to each station. In other words, a station 5 kilometres from a district centroid would get a weight of 1/5 (0.2) whereas a station 100 kilometres from a district centroid would get a weight of 1/100 (0.01).

4. Methods

4.1 Estimating the effectiveness of the campaign in reducing malaria burden

Given that the malaria elimination program occurred at the aggregate level in one district of Maputo province, we could compare changes in malaria incidence to other districts using a difference-in-differences (DD) model. DD are often used to estimate treatment effects in such settings by contrasting changes in outcome pre- and -post intervention, for the treatment and control groups. One feature of the DD model is that it can eliminate confounding due to time-invariant differences between treatment and control groups, arising from unobservable factors that might influence malaria incidence. DD also assumes that any macro shocks such as time effects are common to the groups under evaluation. In combination, these two assumptions give the “parallel trends” assumption on which the validity of the DD model is based.

Figure 2 presents the trends in weekly malaria incidence in Magude and the control districts by age group from 2010 onwards. Both graphs indicate relatively stable malaria trend in the control districts. However, Magude shows a downward trend in incidence over time, even prior to the elimination campaign. The lack of a visible parallel trend between treatment and control groups calls into question the applicability of the standard DD model in our case. Accordingly, we employ the synthetic control method (SCM), which allows for greater flexibility in the estimation of the impact of the malaria elimination campaign (Abadie, Diamond, & Hainmueller, 2010, 2015).

Under the SCM, we construct a weighted combination of potential control districts, the synthetic control, using the districts that best approximate the most relevant characteristics of malaria incidence in Magude before the intervention. These characteristics must be predictors that are not affected by the elimination campaign, can include pre-intervention values of the outcome, and can be either time varying or time invariant. Our analysis covers the period October 2013 to March 2017.

Our data consists of districts $j=1\ldots,J+1$ with malaria outcomes for time periods $t=1,\ldots.,T$. For the sake of exposition, we assume the first unit is Magude $(j=1)$ and exposed to the elimination campaign, leaving us with J control districts. In our application $J=17$, $j=1,\ldots.,17+1$ In the approach the intervention occurs at time-period T_0+1 such that time periods $1,2\ldots.,T_0$ are pre-elimination and $T_0+1,T_0+2,\ldots.T$ are intervention periods. We use time series data on weekly cases from October 2013 to March 2017 with the intervention beginning with IRS in August 2015.

Two potential outcomes can be defined: First, the 'unobserved' counterfactual outcome Y_{jt}^{N} for Magude at time *t* if Magude had not been exposed to the elimination campaign; and second, Y_{jt}^{I} the outcome for Magude under the elimination campaign. Our aim was to estimate the effect of the campaign in Magude during the intervention periods. This effect is defined as the difference between

the potential outcomes:$\alpha_{jt} = Y_{jt}^{I} - Y_{jt}^{N}$ for time-periods $T_0+1, T_0+2, \ldots T$ (August 2015 – March 2017). We apply the SCM to generate an estimate of Y_{jt}^{N} in the intervention period.

Following Abadie et al (2010) we assume a linear relationship between the outcome variable and predictors, to define the observed outcome as:

$$Y_{jt}^{I} = Y_{jt}^{N} + \alpha_{jt} D_{jt}$$

$$Y_{jt}^{N} = \delta_t + \lambda_t \mu_j + \theta_t Z_j + \epsilon_{jt}$$

Where δ_t represents a time fixed effect, μ_j is a vector of time-invariant unobserved predictor factors with time varying coefficients λ_t. Z_j is a vector of observed predictor variables, which in our case included pre-intervention - malaria incidence during the Malaria season (January to March), precipitation, temperature, coverage of LLINs and precipitation in 2016 (post intervention). Since precipitation is unlikely to be affected by malaria incidence, we include precipitation in 2016 (post intervention) to capture the effects of the drought in Mozambique during that year. D_{jt} is a binary indicator variable taking the value of 1 if the district is Magude (treated) and 0 for the control districts. The SCM as specified above allows the effect (λ_t) of the unobserved predictors μ_j to vary over time, relaxing the parallel trend assumption of only time-varying unobservables in the difference-in-differences approach.

We construct the synthetic control as a weighted combination of control districts that best approximate the pre-intervention characteristics of Magude. We estimate a vector $(J \times 1)$ of weights $W = (w_2, \ldots, w_{J+1})'$ such that each $w_j \geq 0$ and the weights, sum to 1 and w_j is the contribution of each control district to the formation of the synthetic control. The unobserved counterfactual for

Magude is estimated as a weighted linear combination of control unit outcomes, $\widehat{Y}_{1t}^{N}=\sum_{2}^{J+1} w_j Y_{jt}$. If the weighted values of the included predictor variables and pre-treatment outcomes for control districts are similar to those of Magude (i.e. $\sum_{2}^{J+1} w_j Z_j = Z_1$ and $\sum_{2}^{J+1} w_j Y_{jt} = Y_{1t}$) and if the outcomes are a linear combination of observed and unobserved predictor factors, then our estimated treatment effect $\hat{\alpha}_{1t}$ is an unbiased estimate of the true treatment effect α_{1t}.

To implement the SCM numerically, we estimate a vector of weights W^{i} to minimize the discrepancy in predictors between Magude and the synthetic control. This discrepancy is defined as a metric of distance $\sqrt{\left(X_1 - X_0 W\right)' V \left(X_1 - X_0 W\right)}$, where X_1 is a $k \times 1$ vector of predictor variables described earlier for Magude and X_0 is the corresponding vector of dimension $k \times j$ for control districts. The vector V is a $k \times k$ symmetric and positive semidefinite matrix which allows different weights to each of the predictor variables depending on their importance in generating the outcome. Both W and V were chosen to minimize the root mean squared prediction error (RMSPE) of pre-intervention outcomes (see Abadie et al. (2015)for further details).

Valid implementation of the SCM requires that the synthetic control closely reproduce the pre-intervention predictors of malaria incidence in Magude. This can be evaluated by examining the root mean squared prediction error (RMSPE) in the pre-intervention period. In the post-treatment period, the SCM provides the counterfactual situation for Magude, in the absence of the elimination campaign. The impact of the campaign is estimated by comparing the outcome trend of the synthetic control with Magude in the post-intervention period.

Compared to DD and other regression-based quasi-experimental methods, the SCM has several advantages: using a weighted average of control units, the SCM makes explicit the relative

contribution of selected control districts to the counterfactual; the similarities between Magude and the synthetic control can be evaluated by comparing pre-intervention outcomes and predictors; the weights allocated to the control units are restricted to sum to one, providing a safeguard against extrapolation; and most importantly for our purposes, the SCM allows the effects of unobserved factors on malaria incidence to vary with time, relaxing the parallel trend assumption of DD discussed earlier.

4.2 Statistical significance of estimated effects

A limitation of SCM is that it does not allow assessing the significance of the results using commonly used (large-sample) inferential techniques since the number of control groups is small. We conducted inference using a set of placebo experiments, where we sequentially apply the SCM to each of the control units to generate a distribution of treatment effects. By construction, this approach provides exact inference irrespective of the number of control districts, however, the power of the test increases with the number of available control units. We compare the distribution of placebo effects to the treatment effect for Magude and calculate the p-value of the one-sided test as the proportion of placebo effects which were at least as extreme in value as the estimated effect for Magude. We note that, by construction, the smallest the p-value is likely to be when Magude has the largest treatment effect is 1/18=0.056. This method of inference is similar to permutation inference (Lehmann, 1997), where a test statistic is estimated by random permutations of assigning a particular unit to treatment or control. This approach does not generate confidence intervals and the interpretation is restricted to whether the estimated effect is large or not compared to the distribution of the placebo effects.

5. Results

In this section we present our estimates of the average causal impact of intensified malaria elimination activities, including free door-to-door MDA on malaria burden in Magude.

5.1 Coverage and uptake

With a population of approximately 50,000 people in 11,000 households, universal IRS deployed between August-October of 2015 reached 92.6% of targeted houses. MDA program data indicate the

first and second MDA rounds, conducted between November 2015 and January 2016, treated approximately 70% and 55% of the population at risk, respectively. The second round of IRS in Magude achieved 93.6% coverage and the third and fourth MDA rounds in Magude were delivered December 2016 -February 2017, treating around 67% of all the population at risk. It should be noted that universal coverage of LLINs was achieved by MoH campaign in 2014 across Mozambique. This does mean that any impact we observe in 2016-17 may be the cumulative effect of LLINs with IRS and MDA.

5.2 Main results

Table 1 shows the weights of each control district in the construction of synthetic Magude. Synthetic Magude for children below 5 years is a weighted average of Boane, Chicualacuala, Chigubo, Mablane, Matutuine and Xai-Xai districts; while for those 5 years and above it is a weighted average of Chigubo, Mablane, Namaacha and Xai-Xai districts. All other districts in the control pool obtain zero weights.

Table 2 compares the predictor characteristics of weekly malaria incidence in Magude to those of synthetic Magude. Overall, results suggest small differences between synthetic Magude and Magude in predictor variables. Figures 3a and 3b display the weekly incidence trajectory of Magude and its synthetic counterpart for the period October 2013 – March 2017. Synthetic Magude closely reproduces the malaria trend in Magude in the pre-elimination period. This good fit is also reflected in the pre-elimination RMSPE of 2.13 cases per week for the 0-4 years model and 1.65 cases per week for 5+ years. During the intervention period there is a clear difference in the trajectories indicating a reduction in malaria. Figures 4a and 4b display the pre-intervention incidence trajectory (Oct 2013-July 2015) for the control districts included in generating synthetic Magude. Generally, the included districts all show the pre-intervention downward trend in malaria seen for Magude.

Between August 2015 and March 2016 the average treatment effect was a reduction in weekly malaria incidence by 4 cases per 1000 in children 0-4 years and by 2 cases per 1000 in those aged 5+ years

(Table 3). Model estimates show a reduction of 437 (0-4 years) and 1502 (5+ years) malaria cases during the peak of the malaria season (January-March) 2016 and 685 (0-4 years) and 2720 (5+ years) between January-March 2017.

If synthetic Magude had failed to fit malaria incidence for Magude in the weeks before the elimination campaign, we would interpret that much of the post-treatment gap between real and synthetic Magude was artificially created due to lack of fit. Similarly, placebo estimates of the treatment effect do not provide accurate estimates if their fit is poor prior to August 2015. Abadie et al. (2010) propose excluding districts beyond a certain level of pre-August 2015 RMSPE. We apply a strict cut-off and include only those districts that we can fit almost as well as Magude in the period before August 2015, that is, those districts with pre-RMSPE not higher than 3 times the pre-RMSPE of Magude. We find one district (Massengena) had a RMSPE larger than this cut-off and eliminate it from the inference considerations.

The 2016 result for 0-4 years is robust to placebo testing, as none of the placebo experiments for the control districts shows treatment effects larger than those for Magude; this is not the case for the 5+ age group (See Figures 5 and 6). Between August 2016 and March 2017, the estimated treatment effect was larger, but these results were not robust to placebo tests. In terms of magnitude, the effect in Magude was only exceeded by two of the control districts.

Similar findings were obtained in a cluster randomized controlled trial (RCT) estimating the effectiveness of MDA with DHA/PPQ in Zambia (Eisele et al., 2016). In that study, while the number of malaria cases significantly declined after MDA in low-transmission areas, the drop was not significant in areas of high transmission (as is the case of Magude).

5.3 Placebo test with diarrhoea outcomes

In this test, we conduct a form of "falsification exercise" where we investigate whether the observed reduction in malaria incidence was generated by the malaria elimination campaign or whether there

were other structural factors that may have resulted in the observed reduction. Such factors may also influence other health outcomes such as diarrhoea in young children. We use data on diarrhoea cases amongst children 0-5 years taken from the same data source. However, these outcomes are only available for the district of Maputo province (which includes Magude district) up to December 2016. Nevertheless, this allows us to re-estimate the SCM using diarrhoea cases as the outcome and the same subset of control districts in Maputo province.

We find no evidence of an effect on diarrhoea cases. The graphical representation of SCM (Figure 7) shows no divergence in the intervention period. This gives us greater confidence in the robustness of our results for the malaria elimination campaign.

5.4 Implications of our findings

A number of experimental studies in economics have demonstrated that heavy subsidization is required to generate high demand for preventative malaria strategies (Pascaline Dupas, 2014). However, MDA is an invasive strategy whose private benefits are not easily identifiable and hard to learn over time. We show over two years that free door-to-door MDA accompanied by community sensitization activities results in high coverage, remaining at around 67-70%. This is, however, lower than the recommended 80% required to break malaria transmission. But the question is also whether high uptake translates to drug intake. This requires information on whether individuals take their pills after it was provided to them. This can be evaluated either from self-reports of adherence or bio-makers, neither of which are available in aggregate data. However, adherence should be reflected in malaria incidence. Consistent with pricing studies we find that people need not have paid for something to value it (Pascaline Dupas, 2014). Our estimates show that over multiple rounds, this level of uptake results in a very large reduction in the incidence of malaria – particularly among those aged 0 to 4. Across age groups during the peak malaria season (January-March) our estimates imply incidence declined by 91.29% and 81.3% in 2016 and 2017, respectively. In comparison with other settings where both coverage and compliance with MDA (for non-malaria diseases) were low, we

believe that in the case of Magude community sensitization alongside the MDA was key to lowered recipients' fear of the drugs and sustained compliance over time.

It is important to clarify that while elimination is defined as zero local cases, the BES data we use does not distinguish between local and imported cases. Therefore, the few non-zero cases could reflect imported malaria cases. This is likely to be the case as Magude is characterized, on top of the normal movement of people across districts, by the migration of seasonal sugarcane workers.

Assuming a constant impact of imported malaria, the larger decline in 2016 is likely to be the combined effects of LLINs distributed in 2014, which has a life of three years, slightly higher MDA coverage of the population at risk and the drought in Mozambique in 2016. In 2017, a year with normal rainfall, less effectiveness of LLINs and with slightly lower MDA coverage, the decline in incidence was smaller. Our finding is consistent with the predictions of a consensus study that put together 4 models focusing on the impact of MDA with a drug having similar characteristics as DHA/ PPQ (Brady et al., 2017). The consensus study predicted an immediate decline in malaria prevalence after MDA, but also that the decline would be transient if no other long-term intervention is implemented such as LLINs. While our results from the second year indicate two other districts had larger declines in incidence that year, it is important to emphasize that to break transmission and achieve elimination, sustained low levels of incidence are required. In the absence of MDA, this cannot be guaranteed by just LLIN and IRS as reflected in the historic trends we see for the region.

Regardless of the declining effectiveness, our study provides clear evidence that MDA in combination with high coverage of control strategies in the context of elimination, results in a very large reduction in the malaria burden. To our knowledge, this study is the first quasi-experimental evaluation of a recent elimination initiative using routine national surveillance data on health indicators. Given the focus over the last decade on malaria elimination with both large- and small-scale campaigns across the globe – such approaches offer a rigorous and inexpensive alternative to randomized-control trials. To the extent that observational data is widely (and often publicly) available, that true experimental

approaches are often not feasible, and that introspective control methods (i.e. the "before and after" comparisons regularly used in program evaluations) are unsuitable for evaluating causal impacts, approaches like the SCM are an excellent alternative for the evaluation of malaria elimination initiatives. We believe that the approach is not only suitable for the estimation of the impact of the intervention in question, but also generalizable to malaria elimination campaigns globally.

5.5 Costs

This section presents estimates of the costs and costs per outcome of the malaria elimination package. The total implementation package over two years, consisting of universal IRS, followed by community sensitization and two population-wide MDA rounds per year, together with a strengthened surveillance system, cost US$3.6 million. With the average district population (54,195), this is equivalent to a cost of US$66 per person targeted. Costs were mainly driven by the 4 rounds of MDA, which together with the community sensitization costs represent 70% of the overall resources used. In Table 5 we present the costs of the MDA component alone. Considering MDA and community sensitization costs alone, the average cost per person covered and per person treated per round are US$17 and US$21 respectively (Table 6). These unit costs are much higher than might be expected. One reason for this is the high cost of the drug. DHA/PPQ was bought at a cost of around US$4 per person treated per round. Typically in SSA malaria drugs are provided by the Global Fund, purchased at significantly lower negotiated prices. DHA/PPQ has never been purchased by the Global Fund for SSA. The cost of such elimination activities will to a large extent depend on the funders/international organizations and their capacity to negotiate and purchase large quantities. It is also worth highlighting that the costs we present in Table 5 are full economic costs. This includes costs of around 500 personnel recruited for door-to-door delivery of the intervention. Typically, other such health campaigns in SSA rely on volunteers whose shadow price are not usually included in estimating costs and cost-effectiveness. If the MDA campaign was integrated within other interventions implemented at the community level by the government (i.e LLIN distribution or other sensitization activities), costs could be drastically reduced from the economies of scope generated by a shared delivery platform.

Taking into consideration the effectiveness figures presented in this analysis, the elimination initiative averted a total of 12,224 malaria cases over the intervention period, for a cost of US$293 per case averted. We emphasize that these figures present the costs in terms of process outcomes and do not represent estimates of cost-effectiveness. In considering cost-effectiveness of elimination campaigns it is vital to consider the long-term health and non-health benefits of eliminating malaria in a population, in addition to the cost-savings from treating fewer malaria cases.

6. Conclusion

The control of malaria as of other non-vaccine preventable infections, relies on the repetition of interventions: provision of MDA, LLINs and IRS needs to happen periodically in order to break transmission and maintain low levels of incidence over sustained periods. However, achieving elimination may require annual or bi-annual free drug delivery over many years with consequent issues of financial sustainability which adds to the high risk of failure intrinsic to elimination (Barrett, 2004, 2013). Effectiveness, affordability and sustainability of elimination campaigns are among the main concerns of funders, stakeholders and policymakers (Acharya, Diaz-Ortega, Tambini, de Quadros, & Arita, 2002; Babigumira et al., 2011).

Our evaluation of a malaria elimination initiative in a district of Southern Mozambique using the synthetic control method shows MDA is an effective strategy to dramatically reduce malaria incidence in moving towards elimination. The SCM allowed for the construction of a realistic counterfactual scenario with which to compare the observed weekly malaria incidence since the intervention started. In contrast to the before-and-after approach used by many malaria intervention effectiveness evaluations(World Health Organisation, 2016), the SCM better handles issues such as a general decline in malaria in the area and effects of time-varying unobservable factors that might influence malaria outcomes, such as economic development.

Our cost estimates show how expensive elimination campaigns can be and to some extent cast doubts on the financial feasibility of elimination. However, the economic viability of malaria elimination campaigns should be analysed over a larger time span, taking into consideration the potential economies of scale and scope that might accrue when expanding large-scale interventions, as well as capturing the potential health, economic and wider social benefits that accrue in the mid and long run from eliminating the disease.

The limitations of our study are two-fold. First, we rely on surveillance malaria cases reported at the health facility level, which is an incomplete and imperfect proxy for true malaria infection incidence, since health-seeking behaviour is especially low in low-income countries settings and may be different across geography and time. Specifically, it is reasonable to assume that the awareness-raising associated with the campaign may have increased health-seeking behaviour, thereby resulting in our underestimation of the campaign's true effect. Second, the health facility registries from which we gathered data are themselves imperfect; we have no mechanisms by which to validate the entirety of the data. Still, BES data offers the best country-wide comparison of malaria trends at a granular level (weekly and by district).

Despite these limitations, this study provides important evidence pertaining to the effectiveness of a malaria elimination initiative in a high-transmission setting. Additionally, it demonstrates the utility of quasi-experimental approaches not commonly used in public health and, the use of routine surveillance data for the estimation of similar initiatives' effectiveness.

We conclude that given the sustained take-up and large reductions we see in malaria incidence over multiple years, public provision of MDA alongside existing control strategies is a way forward towards potential elimination. Given malaria elimination is only considered a viable target in countries with sustained malaria control and low levels of incidence, subsidization through free provision is a worthwhile effort to eliminate malaria.

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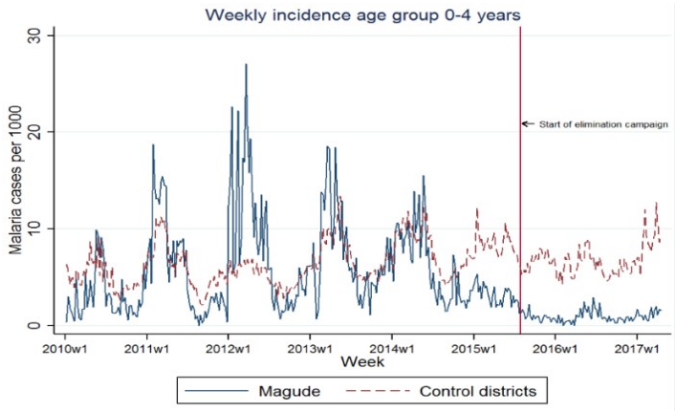
Figures and Tables

Figure 1: Map of Mozambique showing treatment and control districts



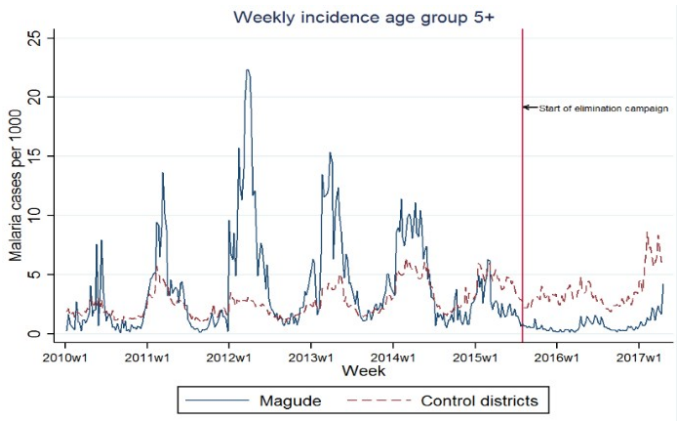


Figure 2: Trends in weekly incidence by age group

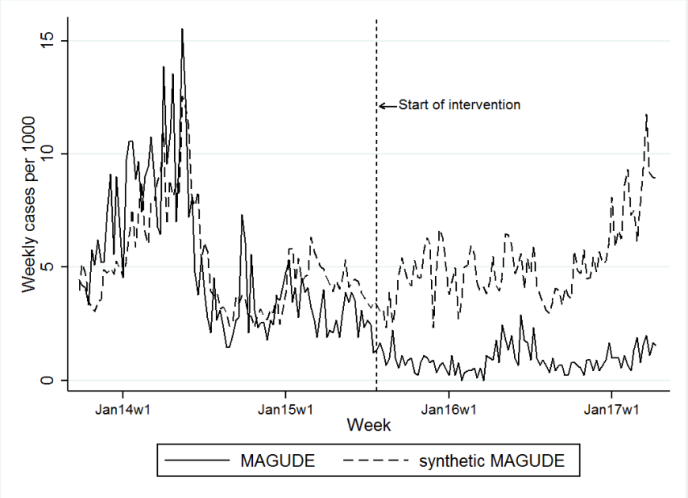

Weekly cases per 1000
0
5
10
15
Start of intervention
Jan14w1
Jan15w1
Jan16w1
Jan17w1
Week
MAGUDE
synthetic MAGUDE

Figure 3a:Trends in malaria incidence: Magude versus synthetic Magude ages 0-4 years

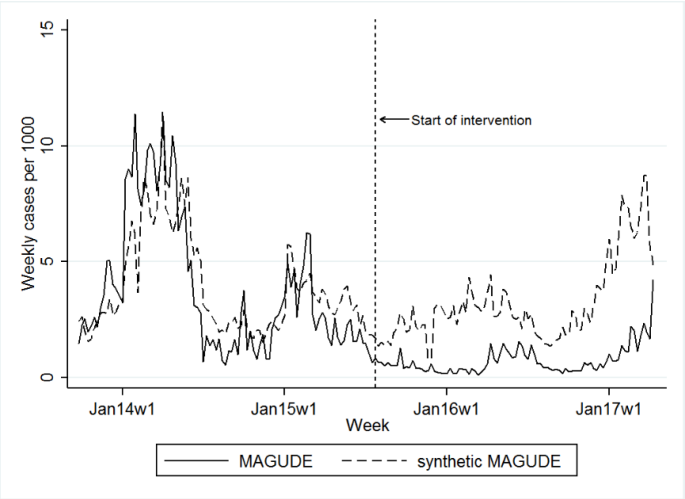


Figure 3b: Trends in malaria incidence: Magude versus synthetic Magude ages 5+ years

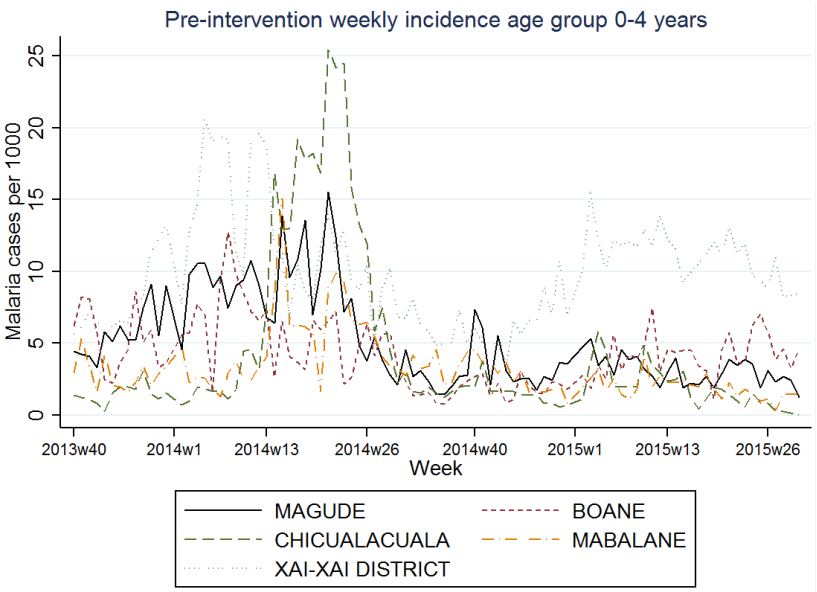


Figure 4a: Pre-intervention malaria incidence 0-4 years in control districts selected for synthetic Magude

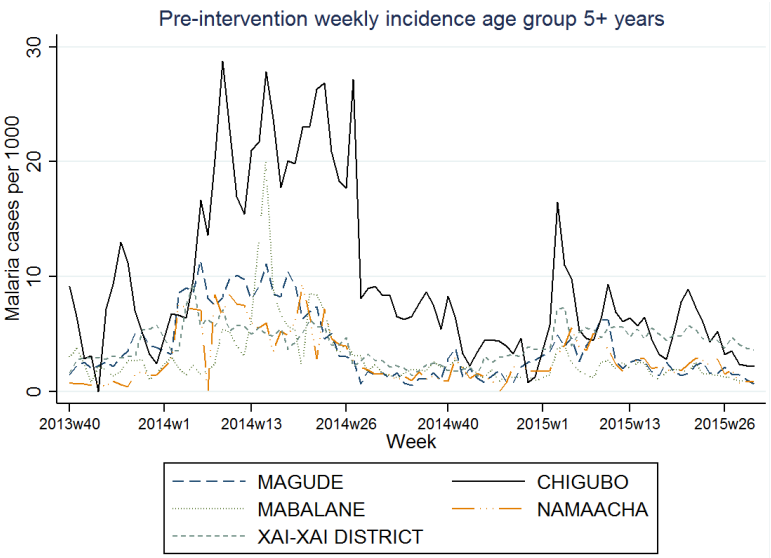
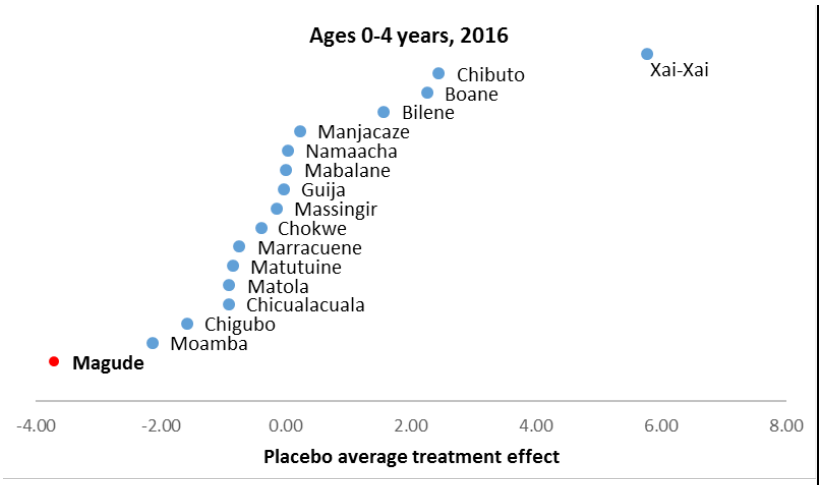


Figure 4b: Pre-intervention malaria incidence 5+ years in control districts selected for synthetic Magude


Ages 0-4 years, 2016
Xai-Xai
Chibuto
Boane
Bilene
Manjacaze
Namaacha
Mabalane
Guija
Massingir
Chokwe
Marracuene
Matutuine
Matola
Chicualacuala
Chigubo
Moamba
Magude
-4.00
-2.00
0.00
2.00
4.00
6.00
8.00
Placebo average treatment effect

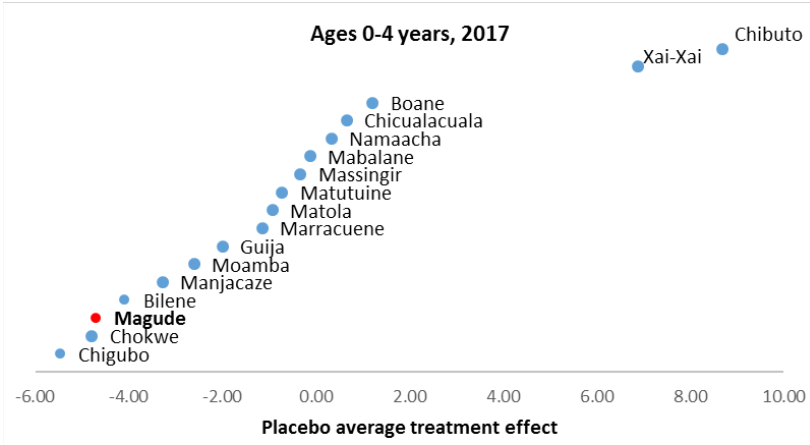
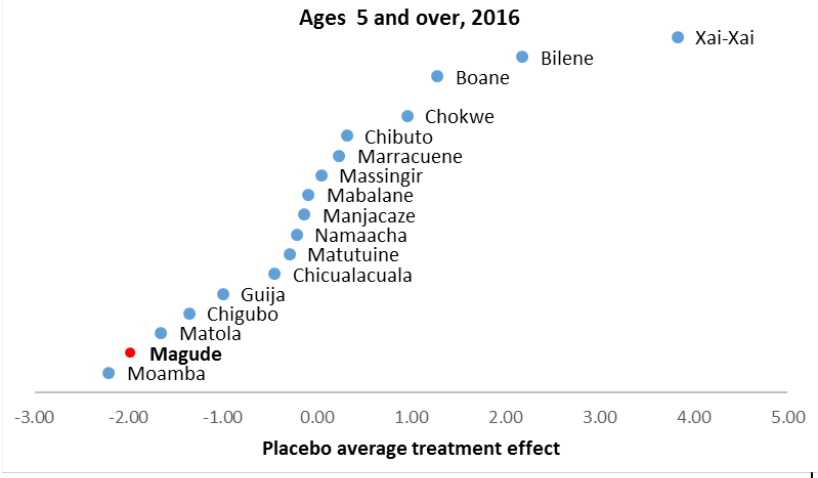

Ages 0-4 years, 2017
Chibuto
Xai-Xai
Boane
Chicualacuala
Namaacha
Mabalane
Massingir
Matutuine
Matola
Marracuene
Guija
Moamba
Manjacaze
Bilene
Magude
Chokwe
Chigubo
-6.00
-4.00
-2.00
0.00
2.00
4.00
6.00
8.00
10.00
Placebo average treatment effect

Figure 5: Placebo treatment effects 0-4 years



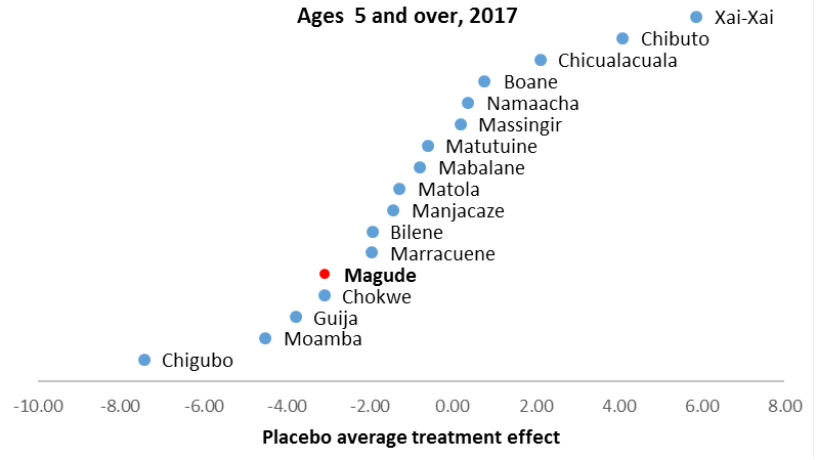


Figure 6:Placebo treatment effects ages 5+

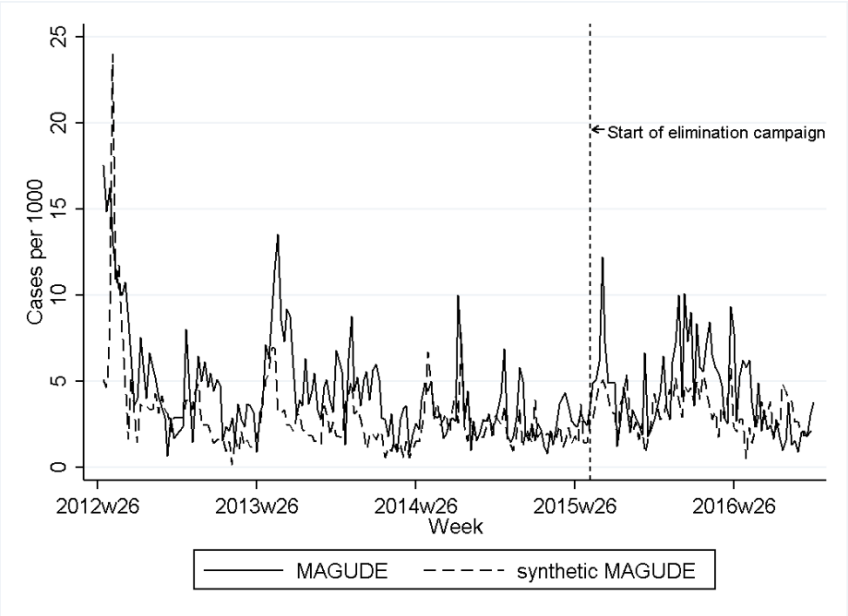


Figure 7: Trends in diarrhoea cases: Synthetic Magude versus real Magude

Table 1: Synthetic Weights for Magude

	Age 0-4 years	Age 5 + years
Bilene	0.00	0.00
Boane	0.22	0.00
Chibuto	0.00	0.00
Chicualacuala	0.19	0.00
Chigubo	0.01	0.10
Chokwe	0.00	0.00
Guija	0.00	0.00
Mabalane	0.27	0.26
Manjacaze	0.00	0.00
Marracuene	0.00	0.00
Massagena	0.00	0.00
Massingir	0.00	0.00
Matola	0.00	0.00
Matutuine	0.07	0.00
Moamba	0.00	0.00
Namaacha	0.00	0.35
Xai-Xai	0.24	0.29

Notes: The synthetic weight is the district weight assigned by the synthetic control method.

Table 2: Predictor means

	Age 0-4 years		Age 5 + years	
	Magude	Synthetic Magude	Magude	Synthetic Magude
Incidence (Jan-Mar 2015)	3.65	5.1	4.02	4.12
Incidence (Jan–Mar 2014)	8.87	6.93	8.53	6.29
LLIN coverage	24.82	24.77	24.83	25.22
Precipitation (pre-intervention period)	1.71	1.74	1.7	1.71
Temperature (pre-intervention period)	24.52	24.51	24.52	24.49
Precipitation (post-intervention period)	1.84	1.84	1.84	1.83

Notes: Incidence is averaged over the periods Jan 15-Mar 15, Jan 14-Mar 14, LLIN coverage/Precipitation/ Temperature (pre-intervention period) are averaged over the entire pre-intervention period, Precipitation (post-intervention period) is averaged over 2016.

Table 3: Average treatment effect

	Age 0-4 years	Age 5+ years
2016 (Aug-Mar)	-3.71	-1.98
2017 (Aug-Mar)	-4.70	-3.06

Table 4: Estimated reduction in number of cases by age group during Malaria season

	Ages 0-4 years	Ages 5+ years
Number of cases (Jan-Mar 2016)	437	1,502
Number of cases (Jan-Mar 2017)	685	2,720

Table 5: MDA costs per budget category (over 4 rounds), in USD 2015

Budget category	**Costs (in USD, 2015)**	**Contribution**
Personnel	1,044,191	43%
Infrastructure	37,372	2%
Equipment	11,839	0%
Drugs and supplies	501,293	21%
Office material	41,764	2%
Training and supervision	31,388	1%
Transport	738,866	30%
IT	32,689	1%
Total cost	**2,439,402**	**100%**

Table 6: Cost per outcome, in USD, 2015

Outcome	**Number (average/round)**	**Rounds**	**Cost/outcome**	**Unit**
People targeted	54,195	NA	$66	Per person (all costs)
People reached with MDA	38,396	4	$17	Per person per round (MDA+community mobilization)*

People treated with MDA	32,284	4	$21	Per person per round (MDA+community mobilization) *
Households covered with IRS	11,463	2	$30	Per household per round
Cases averted	12,224	NA	$293	Per case averted (all costs)

* Note: the antimalarial (DHA-PQP) drug cost -including shipment- costs 4 USD per person treated per round